

Vascular Disease Management

Increased Cutaneous Sensibility in Patients with Diabetic Neuropathy Utilizing a Pharmacological Approach — Clinical Case Evidence

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Introduction

Diabetes mellitus (DM) has reached epidemic proportions within the last quarter century in the United States and throughout the world — the number of diagnosed individuals doubled^{1,2} between 1992 and 2002. Diabetes affects more than 7% of the population of the United States or 20.8 million people, and more than 6.2 million people remain undiagnosed.^{1,3}

Diabetes and its complications have a significant impact on morbidity and mortality by virtue of the macrovascular, microvascular and metabolic sequelae associated with the concomitant increased risk of heart disease, hypertension, stroke, renal disease, peripheral vascular disease, peripheral neuropathy, foot ulcerations, chronic lower-extremity infections and nontraumatic limb loss, representing an annual cost of \$132 billion.¹

From a demographic point of view, the increasing high-risk populations reflect the anticipated increased prevalence of diabetes as the over-age-60, non-Hispanic black, Hispanic American and Native American groups increase in

population percentage. This directly corresponds to the attendant rise of “pre-diabetes” and type 2 diabetes.⁴

Diabetic peripheral neuropathy (DPN) is estimated to be present in 50% of individuals afflicted with DM. Painful diabetic neuropathy (DPNP) affects 11% of patients with DPN. Diabetic peripheral neuropathy is associated with a significant impact on quality of life, impaired activities of daily living, sleep disruption, imbalance and instability of gait with increased fall risk and psychosocial disorders.⁵

Although the prevalence of DPN is significant and ever increasing, and DPN is the leading cause of diabetic foot ulceration and non-traumatic limb loss, little consensus regarding the pathophysiology, diagnostic protocols and primary treatment choices exists.^{6,7} The prevalence of DPN increases with duration of diabetes, poor glycemic control and patient age.⁸ Although it remains a challenge to the practitioner, DPN can be diagnosed and managed on the basis of a thorough medical history and physical exam. The absence of the typical descriptors offered by patients for

neuropathy (eg, feels “asleep,” “dead” numbness, tingling, pricking) and neuropathic pain (burning or knife-like pain, electrical sensations, hurting, throbbing, squeezing, constricting, allodynia) does not necessarily rule out DPN nor does their presence confirm it. Nondiabetic causes for neuropathy and/or pain (eg, alcoholism, thyroid disorders, anemia, vitamin deficiencies, connective tissue disorders, spinal compression radiculopathy, local compression neuropathy [eg, tarsal tunnel syndrome], polyneuropathy, metastatic disease, infection, toxic substances) must be ruled out.

Key elements in the diagnosis of DPN are the establishment of DM or impaired glucose tolerance (IGT) via a 2-hour oral glucose tolerance test (OGTT), assessment of pain characteristics and detection of the presence of neuropathy with use of a monofilament or 128-Hz tuning fork.⁹ These techniques are of limited value as they lack sensitivity and reliability compared to other quantitative sensory testing modalities available, such as the vibrometer and biothesiometer. In order to diagnose abnormal nerve

conduction, there must be 2 separate nerves with abnormal conduction velocities or an abnormal quantitative sensory test (QST).¹⁰ A valuable tool for obtaining the differential diagnosis and the degree of neuropathy/neural damage is the Pressure Specified Sensory Device™ (PSSD). The PSSD, invented by A. Lee Dellon, MD, professor of Plastic Surgery and Neurosurgery at the Johns Hopkins School of Medicine, can identify the earliest degree of nerve damage/sensory loss as compared to other modalities including the Semmes-Weinstein monofilament and electromyography/nerve conduction velocity (EMG/NCV) studies. The PSSD is at least as sensitive as traditional electrodiagnostic studies and is not invasive or painful.¹¹⁻¹⁶ Additionally, it may be used to measure neural response to treatment.¹⁵

The diagnosis of DPN/DPNP is just the beginning. This multifaceted complication of diabetes is generally managed symptomatically with an array of medications, with only 2, duloxetine and pregabalin, currently approved by the US Food and Drug Administration (FDA) for the treatment of DPNP, while “off-label” use of other agents, including tricyclic antidepressants, has proven helpful. As with all medications, choice must be made in concert with known adverse effects, patient comorbidities and, too often, the financial requirements to maintain appropriate dosage.⁶

Despite decades of intense research and study, no clear pathophysiological understanding of diabetic neuropathy exists; however, many pathological pathways have shown some common denominators that have directed even further research into alternate pharmacologic interventions. The physiologic codependence of the peripheral

nerve and its attendant microvascularization is the first sign of pathological changes that result in an ongoing progressive cycle of microvascular and neural dysfunction resulting ultimately in axonal death and an array of symptoms for the patient as this neurovascular disease progresses.

The role of nitric oxide (NO) in diabetic neuropathy and the distal microvasculature is becoming better understood as research in this area intensifies. Reduced NO has been shown to disrupt normal cellular oxidation thus resulting in direct endothelial injury and dysfunction. There also is a relationship between elevated homocysteine levels and patients with type 2 diabetes. The essential amino acid found in dietary proteins, methionine, is metabolized, and homocysteine, an intermediate sulfur-containing amino acid, is a product of that intracellular metabolic process.¹⁷ Elevated homocysteine levels exhibit toxic effects upon the vascular endothelium by reduced NO availability and disrupted cellular oxidation.¹⁸ Normal homocysteine metabolism requires remethylation and transsulfuration with vitamin B6, vitamin B12 and folate as essential biochemical cofactors.

Research has demonstrated that the bioavailability of NO increased with high-dose, short-term folate therapy, resulting in improved endothelial function in patients with type 2 diabetes.^{19,20} Oral L-methylfolate, or (6S)-5-methyltetrahydrofolate (5-MTHF), the metabolically active form of folic acid, has been shown to be 7 times more bioavailable and 3 times more effective in lowering serum homocysteine than naturally occurring folic acid.^{20,21} L-methylfolate bypasses the complex biochemical pathways for the conversion of folic acid in order for it to become active. It should be noted that 40%–50% of the population

are genetically incapable of completely converting folic acid into L-methylfolate.^{22,23}

Oral methylcobalamin was shown to enhance myelin node genesis and nerve regeneration. One double-blind study demonstrated the regression of some of the symptoms of diabetic neuropathy.^{23,24} The use of vitamin B6, pyridoxal 5'-phosphate, has been shown to reduce the glycosylation of hemoglobin, thus reducing the end-organ damage that glycosylated hemoglobin is postulated to cause. Approximately 30 years ago, the nearly identical symptom complex of diabetic neuropathy and vitamin B6 deficiency was described.²⁵

Nutritional vitamin therapy utilizing folate, vitamin B6 and vitamin B12 to reduce elevated serum homocysteine has been suggested as an acceptable treatment for DPN and DPNP.²⁶ In consideration of the impact of the inverse relationship of serum levels of folate and vitamin B12 and serum homocysteine levels upon NO production and availability, improved endothelial function and vitamin B6 activity, PamLab, LLC (Covington, La) developed Metanx® to treat hyperhomocysteinemia and endothelial dysfunction associated with DPN. This patented formulation of 2.8 mg L-methylfolate, 25 mg pyridoxal 5'-phosphate and 2 mg methylcobalamin should be considered an essential component in the treatment of DPN and DPNP. The only drug interaction that is noted in the package insert for Metanx warns that pyridoxal 5'-phosphate should not be given to patients receiving the drug levodopa because the action of levodopa is antagonized by pyridoxal 5'-phosphate. However, pyridoxal 5'-phosphate may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa. While the concurrent use of phenytoin and folic acid may

Table 1. Patient characteristics

	Patient 1	Patient 2	Patient 3
Age	64	50	64
Sex	Male	Female	Male
Race	White	White	White
Chief Complaints	Burning and numbness	Burning, pain, stocking distribution numbness, sleep disruption	Numbness, pain, imbalance, gait disturbance, sleep disruption
Comorbidities	Hypertension	Hypertension, hypercholesterolemia	Degenerative joint disease, hypertension, hypercholesterolemia
History	Type 2 diabetes, 5 years; DPNP, 5 years	Type 1 diabetes, 29 years; DPN, 29 years; DPNP, 15 years	Type 2 diabetes, 16 years; DPN, 9 years; DPNP, 3 years
% Loss of Protective Sensation	100%	80%	20%
Physical Exam	Trophic skin changes with fissuring, hammer digits, intrinsic muscle wasting	Keratoses, history of ulceration, hammer digits	Keratoses, contracted digits, intrinsic muscle wasting
Pedal Pulses	DP 2/4, bilateral; PT 2/4, bilateral	DP 1/4, bilateral; PT 1/4, bilateral	DP 1/4, bilateral; PT 2/4, bilateral
Subjective Improvement at 3 Months with Metanx Therapy	Less pain, better sleep, 50% overall improvement	No sleep disruption, 40% overall improvement, decreased pain	70% overall improvement, better sleep, less pain
Subjective Improvement at 6 Months with Metanx Therapy	No burning, skin improved, 100% improvement	No symptoms of DPN, 80% overall improvement	No symptoms of DPN, 100% improvement

result in decreased phenytoin effectiveness, no such decreased effectiveness has been reported with the use of Metafolin® (Merck KGaA, Darmstadt, Germany).

The following case reports illustrate the successful use of Metanx in treating DPN and DPNP. Table 1 summarizes the characteristics of all 3 patients.

Case Reports

Patient 1. A 64-year-old white man with hypertension presented with a chief complaint of burning and numbness. His past medical history was significant for type 2 diabetes for 5 years and DPNP for 5 years as well. The patient had 100% loss of protective sensation. Physical examination revealed trophic skin changes with fissuring, hammer dig-

its and intrinsic muscle wasting. Pedal pulses included DP 2/4 bilaterally and PT 2/4 bilaterally.

Baseline PSSD measurements for the great toe pulp were as follows: 1-pt static: left, 68.7 gm/mm² (abnormal pressure threshold) and right, 38.6 gm/mm² (abnormal pressure threshold); 2-pt static: left, 83.6 gm/mm² (abnormal pressure

threshold) with 7.9 mm spacing and right, 54.5 gm/mm² (abnormal pressure threshold) with 7.8 mm spacing. This documented bilateral sensory abnormality is consistent with bilateral tarsal tunnel syndrome and injury at the L4/L5 disk level or L4 or L5 nerve roots. Bilateral involvement of more than one nerve in any extremity suggests a peripheral neuropathy, and severe loss of 2-point discrimination is consistent with axonal loss.

Baseline measurements for the heel (medial) were as follows: 1-pt static: left, 10.5 gm/mm² (abnormal pressure threshold) and right, 6.5 gm/mm² (abnormal pressure threshold); 2-pt static: left, 21.6 gm/mm² with 7.1 mm spacing and right, 14.2 gm/mm² with 7.1 mm spacing. This documented bilateral sensory abnormality is consistent with bilateral tarsal tunnel syndrome and injury to the S1 nerve roots.

Treatment. This patient was instructed to take 1 tablet of Metanx twice daily for 2 weeks and continued a 1 tablet daily-dose regimen throughout the study time period without interruption and continues to do so at press time. All his other medications remained unchanged during the study period, and no other medications were introduced or other procedures performed that might have affected the outcome of this therapy. Despite repeated attempts, he failed at smoking cessation during the 10 years he has been a patient and has recently quit again. It is interesting that 10 years ago on monofilament testing he had a 20% loss of sensation in our initial screening at his first visit, and we have watched his neuropathy progress over the years despite good glycemic control. Along with his sensory loss, the patient experienced burning to numbness to pain with significant nocturnal pain and sleep interruption (somatic symptoms). Also, his autonomic complaints of

sweats, endothelial dysfunction and gastric symptoms progressed during this decade. With the introduction of Metanx, the patient reported initially with significant improvement/reduction of his somatic symptoms within the first 6 weeks of therapy. He related improvements in his autonomic symptoms as well. Inquiry was required to obtain some of the details regarding the patient's autonomic symptoms because of his social reservations. In this case, Metanx demonstrated a relatively prompt affect upon the patient's symptom complex that was accordingly reflected in his neurosensory testing results.

Follow-up. At the 3-month follow-up, the patient reported less pain, improved sleep and 50% overall improvement. Results of the PSSD for the great toe pulp at the 3-month follow-up were as follows: 1-pt static: left, 15.2 gm/mm² (abnormal pressure threshold) and right, 12.6 gm/mm² (abnormal pressure threshold); 2-pt static: left, 44.1 gm/mm² (abnormal pressure threshold) with 7.8 mm spacing and right, 41.2 gm/mm² (abnormal pressure threshold) with 7.8 mm spacing. Results for the heel (medial) were as follows: 1-pt static: left, 3.1 gm/mm² and right, 2.0 gm/mm²; 2-pt static: left, 4.8 gm/mm² with 7.1 mm spacing and right, 7.7 gm/mm² with 7.1 mm spacing. At the 6-month follow-up, the patient reported 100% improvement, no burning and improved skin appearance. Results of the PSSD for the great toe pulp at 6-month follow-up were as follows: 1-pt static: left, 5.0 gm/mm² (abnormal pressure threshold) and right, 2.1 gm/mm² (abnormal pressure threshold); 2-pt static: left, 15.3 gm/mm² with 7.8 mm spacing and right, 5.5 gm/mm² with 7.8 mm spacing. Results for the heel (medial) were as follows: 1-pt static: left, 3.4 gm/mm² and right, 1.4 gm/mm²; 2-pt static: left, 7.2 gm/mm² with 7.1 mm spacing and right, 7.5 gm/mm² with 7.1 mm spacing.

Patient 2. A 50-year-old white woman with hypertension and hypercholesterolemia presented with chief complaints of burning, pain, stocking distribution numbness and sleep disruption. Her past medical history was significant for type 1 diabetes for 29 years, DPN for 29 years and DPNP for 15 years. The patient had 80% loss of protective sensation. Physical examination revealed keratoses, a history of ulceration and hammer digits. Pedal pulses were DP 1/4 bilaterally and PT 1/4 bilaterally.

Baseline PSSD measurements for the great toe pulp were as follows: 1-pt static: left, 16.9 gm/mm² (abnormal pressure threshold) and right, 22.6 gm/mm² (abnormal pressure threshold); 2-pt static: left, 29.5 gm/mm² (abnormal pressure threshold) with 7.8 mm spacing and right, 44.4 gm/mm² (abnormal pressure threshold) with 7.9 mm spacing. This documented bilateral sensory abnormality is consistent with bilateral tarsal tunnel syndrome and injury at the L4/L5 disk level or L4 or L5 nerve roots.

Baseline measurements for the heel (medial) were as follows: 1-pt static: left, 17.1 gm/mm² (abnormal pressure threshold) and right, 27.2 gm/mm² (abnormal pressure threshold); 2-pt static: left, 46.8 gm/mm² (abnormal pressure threshold) with 7.1 mm spacing and right, 58.9 gm/mm² (abnormal pressure threshold) with 7.1 mm spacing. This documented bilateral sensory abnormality is consistent with bilateral tarsal tunnel syndrome and injury to the S1 nerve roots.

Treatment. This patient, at 5' 3" tall and 139 lb with fragile type I diabetes, initially presented with significant somatic symptoms in her feet and hands and was taking gabapentin 300 mg 3 times daily without significant relief of symptoms and attendant drowsiness

side effect. Upon the introduction of Metanx, 1 tablet twice daily for 2 weeks then 1 tablet daily, her symptoms improved dramatically within the first month, allowing her to cease use of gabapentin. While her glycemic control improved and her HgbA1c reduced to 5.6% from 6.6%, she generally reported “just feeling better,” and her overall appearance improved as well. With her sleep deprivation issues addressed without other medications and her pain relieved, her psychosocial attitude had been positively affected as well. There were no other medical changes during the course of this study period that would have affected the outcome.

Follow-up. At the 3-month follow-up, the patient reported no sleep disruption, 40% overall improvement and decreased pain. Results of the PSSD for the great toe pulp at the 3-month follow-up were as follows: 1-pt static: left, 4.3 gm/mm² (abnormal pressure threshold) and right, 1.6 gm/mm²; 2-pt static: left, 6.8 gm/mm² with 7.8 mm spacing and right, 6.6 gm/mm² with 7.8 mm spacing. Results for the heel (medial) were as follows: 1-pt static: left, 2.5 gm/mm² and right, 2.5 gm/mm²; 2-pt static: left, 7.7 gm/mm² with 7.1 mm spacing and right, 7.5 gm/mm² with 7.1 mm spacing. At the 6-month follow-up, the patient reported no symptoms of DPN and 80% overall improvement. Results of the PSSD for the great toe pulp at the 6-month follow-up were as follows: 1-pt static: 1.7 gm/mm² (abnormal pressure threshold) and right, 1.1 gm/mm²; 2-pt static: left, 4.3 gm/mm² with 7.8 mm spacing and right, 3.8 gm/mm² with 7.8 mm spacing. Results for the heel (medial) were as follows: 1-pt static: left, 1.8 gm/mm² and right, 2.4 gm/mm²; 2-pt static: left, 4.9 gm/mm² with 7.1 mm spacing and right, 6.5 gm/mm² with 7.1 mm spacing.

Patient 3. A 64-year-old white man with degenerative joint disease, hypertension and hypercholesterolemia presented with chief complaints of numbness, pain, imbalance, gait disturbance and sleep disruption. His past medical history was significant for type 2 diabetes for 16 years, DPN for 9 years and DPNP for 3 years. The patient had 20% loss of protective sensation. Physical examination revealed keratoses, contracted digits and intrinsic muscle wasting. Pedal pulses were DP 1/4 bilaterally and PT 2/4 bilaterally.

Baseline PSSD results for dorsal web space 1/2 were as follows: 1-pt static: left, 8.9 gm/mm² (abnormal pressure threshold) and right, 21.4 gm/mm² (abnormal pressure threshold); 2-pt static: left, 102.4 gm/mm² (abnormal pressure threshold) with 8.3 mm spacing and right, 97.6 gm/mm² (abnormal pressure threshold) with 8.4 mm spacing. This documented bilateral sensory abnormality is consistent with peripheral neuropathy; bilateral common peroneal nerve entrapment; bilateral foot injuries; and injury to the L5 nerve roots.

Baseline results for the great toe pulp were as follows: 1-pt static: left, 3.8 gm/mm² (abnormal pressure threshold) and right, 3.5 gm/mm² (abnormal pressure threshold); 2-pt static: left, 68.8 gm/mm² (abnormal pressure threshold) with 7.8 mm spacing and right, 99.8 gm/mm² (abnormal pressure threshold) with 7.9 mm spacing. This documented bilateral sensory abnormality is consistent with tarsal tunnel syndrome and injury at the L4/L5 disk level or L4 or L5 nerve roots.

Baseline results for the heel (medial) were as follows: 1-pt static: left, 18.2 gm/mm² (abnormal pressure threshold) and right, 16.6 gm/mm² (abnormal pressure threshold); 2-pt static: left, 105.4 gm/mm²

(abnormal pressure threshold) with 12.0 mm spacing (abnormal spacing) and right, 104.7 gm/mm² (abnormal pressure threshold) with 12.0 mm spacing (abnormal spacing). This documented bilateral sensory abnormality is consistent with bilateral tarsal tunnel syndrome and injury to the S1 nerve roots.

Treatment. This very active man had been a patient in the practice for more than 15 years. During the course of his treatment with Metanx, 1 tablet twice daily for 2 weeks then 1 tablet daily, his somatic symptoms gradually improved in the first 8 to 12 weeks, and by 6 months at the study endpoint, there was a visible difference in muscle strength of his legs and feet, intrinsic muscle wasting was significantly reduced and he reported improved gait stability and “feeling more secure” in his activities of daily living. During the course of the study, there were no changes in any of his other medications or any other medical interventions that might have affected the outcome of his Metanx treatment.

Follow-up. At the 3-month follow-up, the patient reported 70% overall improvement, improved sleep and decreased pain. Results of the PSSD for the great toe pulp at the 3-month follow-up were as follows: 1-pt static: left, 2.6 gm/mm² (abnormal pressure threshold) and right, 3.4 gm/mm² (abnormal pressure threshold); 2-pt static: left, 15.9 gm/mm² with 9.0 mm spacing (abnormal spacing) and right, 23.5 gm/mm² with 9.0 mm spacing (abnormal spacing). Results of the PSSD for the heel (medial) were as follows: 1-pt static: left, 4.9 gm/mm² and right, 2.9 gm/mm²; 2-pt static: left, 52.7 gm/mm² (abnormal pressure threshold) with 10.0 mm spacing (abnormal spacing) and right, 52.9 gm/mm² (abnormal pressure threshold) with 10.0 mm spacing (abnormal spacing). At the 6-month

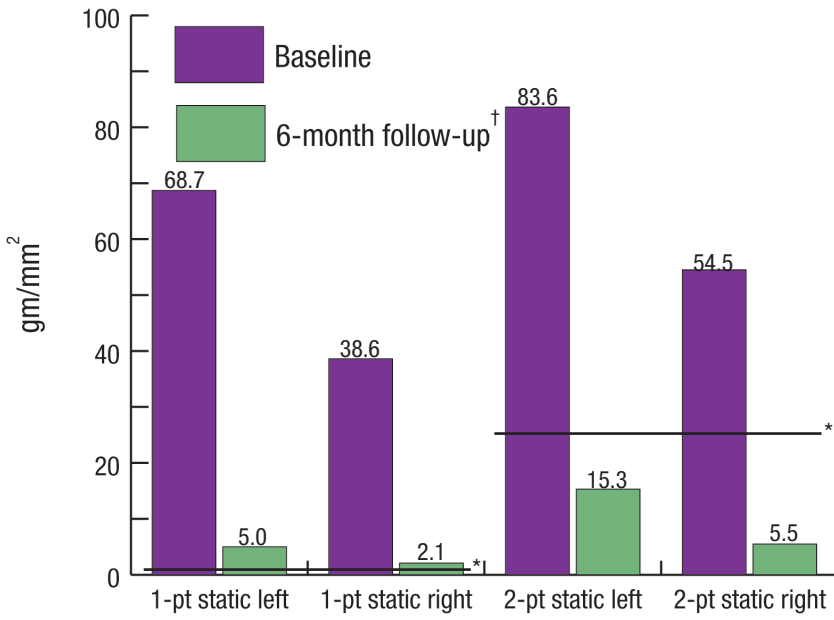


Figure 1. Baseline and 6-month PSSD results for the great toe pulp of Patient 1.

* Normal: 1 pt, 1.6 gm/mm²; 2 pt, 25.7 gm/mm²

† On Metanx therapy

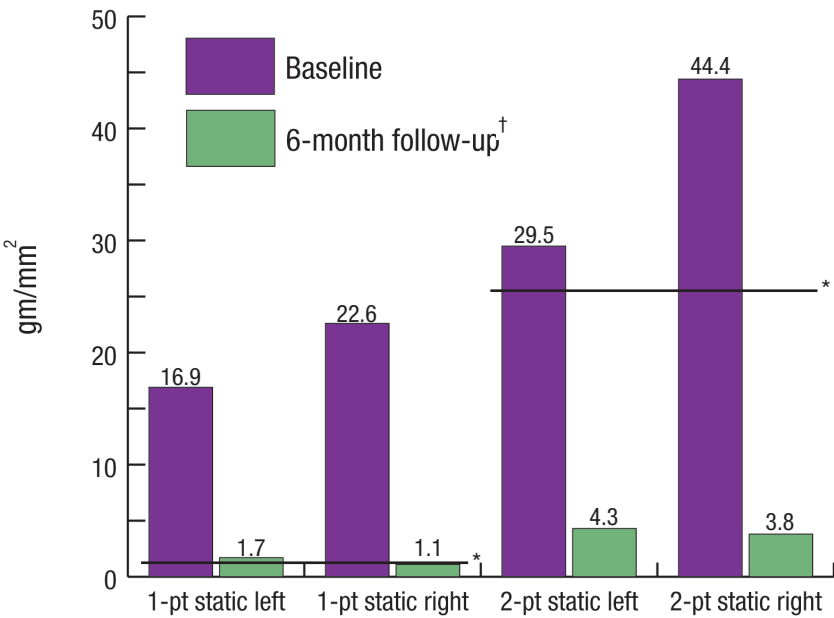


Figure 2. Baseline and 6-month PSSD results for the great toe pulp of Patient 2.

* Normal: 1 pt, 1.6 gm/mm²; 2 pt, 25.7 gm/mm²

† On Metanx therapy

follow-up, the patient reported no symptoms of DPN and 100% improvement. Results of the PSSD for the great toe pulp at the 6-month follow-up were as follows: 1-pt static: left, 0.8 gm/mm² and right, 1.2 gm/mm²; 2-pt static: left, 8.1 gm/mm² with 7.9 mm spacing and right, 11.0 gm/mm² with 7.9 mm spacing. Results for the heel (medial) were as follows: 1-pt static: left, 2.2 gm/mm² and right, 2.1 gm/mm²; 2-pt static: left, 12.8 gm/mm² with 7.1 mm spacing and right, 23.4 gm/mm² with 7.1 mm spacing.

Summary and Conclusion

Herein we have presented 3 cases of patients with DPN. Their response to Metanx therapy was “measured” by use of the PSSD as previously described. We utilized the great toe pulp measurements only for monitoring the response and progress of these patients (Figures 1–3), although other nerves could have been tested during the testing sessions.¹⁶ Additionally, to optimize consistency, the same study was administered by the same examiner in the same room with the same device in each of the studies conducted. With the exception of the addition of Metanx to the patients’ current medical management, no changes occurred in their medical histories.

These 3 cases, unlike others previously described in the medical literature, demonstrate a measured physiologic response and improvement/restoration of peripheral nerve sensitivity along with the subjective improvement of their symptoms. While these results do not occur in all patients with DPN, as Metanx therapy is not a panacea for DPN/DPNP, a significant majority of patients in our practice have demonstrated marked improvement, and we are presently undertaking a prospective study to further evaluate the affects of Metanx on a larger sample of the

DPN population. Another group under study are those patients with post-chemotherapy peripheral neuropathy.

We cannot resist the correlation of the effects of Metanx from a quantitative (PSSD measurements) and qualitative (subjective symptom descriptors) point of view in patient response and recovery for peripheral nerve decompression in the treatment of DPN. In our experience in performing peripheral nerve decompressions to treat diabetic neuropathy, the patient's typical postop recovery in terms of his or her subjective (somatic) and objective (autonomic/PSSD) findings as the postop course ensues and develops is very similar to patients responding to Metanx therapy. With the use of Metanx, evidence seems to confirm the restoration of the endothelial complex, renewing distal perfusion and particularly flow to the peripheral nerve, essentially reversing the steps of the pathophysiology of DPN.

While many pharmaceuticals are offered, FDA approved and available "off label," Metanx provides patients with DPN/DPNP with subjective and quantifiable improvement. Most current literature supports the extrapolation of the effects of this therapy upon diabetic foot wounds.

In consideration of the required dose of 1 or 2 tablets daily, Metanx is a relatively inexpensive, effective agent that should be strongly considered when establishing a treatment plan for any patient with DPN/DPNP.

Glycemic control, medical nutrition, diabetes education, exercise, appropriate use of pharmacological agents, prevention of diabetic foot ulcers and the team approach to diabetes management are major components of the current therapeutic

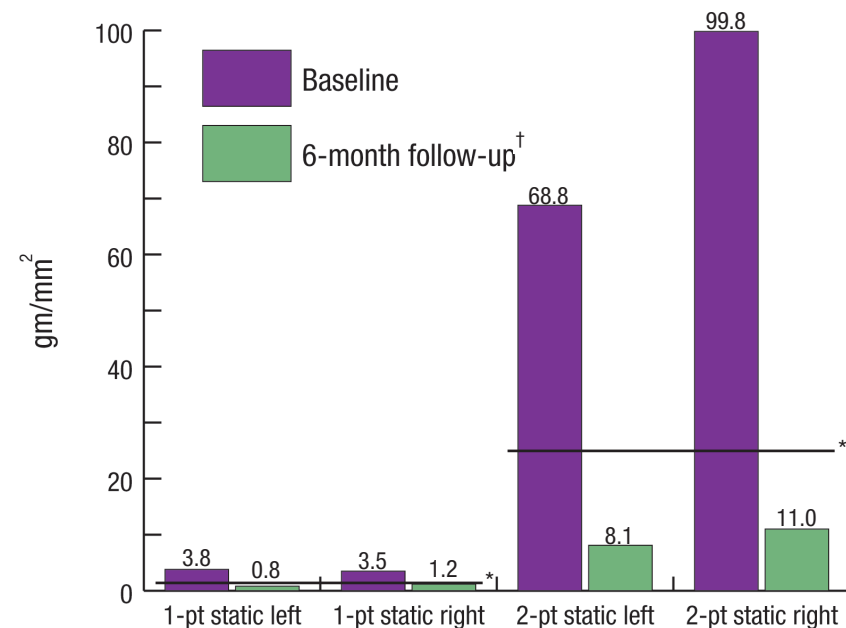


Figure 3. Baseline and 6-month PSSD results for the great toe pulp of Patient 3.

* Normal: 1 pt, 1.6 gm/mm²; 2 pt, 25.7 gm/mm²

† On Metanx therapy

rationale. In addition to these measures, increased public awareness of the diabetes epidemic emphasizing required lifestyle changes has been shown to reduce the onset of diabetes in at-risk populations along with ongoing research and development of new medications and even vaccines to prevent diabetes. The future holds promise that this life-threatening and costly chronic disease will subside in prevalence and morbidity.

References

- Centers for Disease Control and Prevention. National diabetes fact sheet: General information and national estimates on diabetes in the United States, 2005. Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
- International Diabetes Federation and International Working Group on the Diabetic Foot. *Diabetes and Foot Care: Time to Act*. Brussels, Belgium: International Diabetes Federation; 2005.
- National Diabetes Information Clearinghouse. Total prevalence of diabetes in the United States, all ages, 2005. Available at: <http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm#7>. Accessed April 23, 2007.
- Centers for Disease Control and Prevention. Diabetes: Disabling, deadly, and on the rise: At-a-glance, 2005. Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2005.
- Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic peripheral neuropathic pain: Clinical and quality-of-life issues. *Mayo Clin Proc* 2006;81(4 Suppl):S3-S11.
- Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus

- guidelines: Treatment planning and options. Diabetic peripheral neuropathic pain. *Mayo Clin Proc* 2006;81(4 Suppl):S12–S25.
7. Frykberg RG, Zgoni T, Armstrong DG, et al. Diabetic Foot Disorders: A Clinical Practice Guideline (2006 revision). *J Foot Ankle Surg* 2006;45(5 Suppl):S1–S66.
 8. Boulton AJM. Management of diabetic peripheral neuropathy. *Clinical Diabetes* 2005;23:9–15.
 9. Boulton AJ, Gries FA, Jervell JA. Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 1998;15:508–514.
 10. Gries FA, Cameron NE, Low PA, Zeigler D. *Textbook of Diabetic Neuropathy*. New York, NY: Thieme Publishers; 2003.
 11. Dellon ES, Crone S, Mourey R, Dellon L. Comparison of the Semmes-Weinstein monofilament with the Pressure-Specifying Sensory Device. *Rest Neurology Neuroscience* 1993;5:323–326.
 12. Tassler PL, Dellon AL, Scheffler NM. Computer-assisted measurement in diabetic patients with and without foot ulceration. *J Am Podiatr Med Assoc* 1995;85:679–684.
 13. Barber MA, Conolley J, Spaulding CM, Dellon AL. Evaluation of pressure threshold prior to foot ulceration: One-versus two-point static touch. *J Am Podiatr Med Assoc* 2001;91:508–514.
 14. Weber RA, Schuchmann JA, Albers JH, Ortiz J. A prospective blinded evaluation of nerve conduction velocity and the Pressure-Specified Sensory Testing in carpal tunnel syndrome. *Ann Plast Surg* 2000;45:252–257.
 15. Valdivia JM, Dellon AL, Weinand ME, Maloney CT Jr. Surgical treatment of peripheral neuropathy: Outcomes from 100 consecutive decompressions. *J Am Podiatr Med Assoc* 2005;95:451–454.
 16. Wood WA, Wood MA, Werter SA, et al. Testing for loss of protective sensation in patients with foot ulceration: A cross-sectional study. *J Am Podiatr Med Assoc* 2005;95:469–474.
 17. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. *N Eng J Med* 1998;338:1042–1050.
 18. Ambrosch A, Dierkes J, Lobmann R, et al. Relation between homocysteinaemia and diabetic neuropathy in patients with Type 2 diabetes mellitus. *Diabet Med* 2001;18:185–192.
 19. Mangoni AA, Sherwood RA, Asonganyi B, Swift CG, Thomas S, Jackson SH. Short-term folic acid supplementation enhances endothelial function in patients with type 2 diabetes. *Am J Hypertens* 2005;18(2 Pt 1):220–226.
 20. Venn BJ, Green TJ, Moser R, Mann JI. Comparison of the effect of low-dose supplementation of L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: A randomized placebo-controlled study. *Am J Clin Nutr* 2003;77:658–662.
 21. Boykin JV Jr, Baylis C, Allen SK, et al. Treatment of elevated homocysteine to restore normal wound healing: A possible relationship between homocysteine, nitric oxide, and wound repair. *Adv Skin Wound Care* 2005;18:297–300.
 22. Deloughery TG, Evans A, Sadeghi A, et al. Common mutation in methylenetetrahydrofolate reductase. Correlation with homocysteine metabolism and late-onset vascular disease. *Circulation* 1996;94:3074–3078.
 23. Boykin JV Jr. Ischemic vascular disease, nitric oxide deficiency, and impaired wound healing. *WOUNDS* 2006;18(Suppl): S1–S11.
 24. Yaqub BA, Siddique A, Sulimani R. Effects of methylcobalamin on diabetic neuropathy. *Clin Neurol Neurosurg* 1992;94:105–111.
 25. Jones CL, Gonzalez V. Pyridoxine deficiency: A new factor in diabetic neuropathy. *J Am Podiatry Assoc* 1978;68:646–653.
 26. Eikelboom JW, Lonn E, Genest J Jr, Hankey G, Yusuf S. Homocyst(e)ine and cardiovascular disease: A critical review of the epidemiologic evidence. *Ann Intern Med* 1999;131:363–375.

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